PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C08L 53/00 — A2

(11) International Publication Number: **WO 00/12623**

(43) International Publication Date: 9 March 2000 (09.03.00)

(21) International Application Number: PCT/EP99/06219

(22) International Filing Date: 25 August 1999 (25.08.99)

(30) Priority Data:
9818914.5 28 August 1998 (28.08.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TX8 9EP (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: ROUTLEDGE, Carol [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WATERS, David, Martin; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: USE

(57) Abstract

Use of 5-HT_6 receptor antagonists for the preparation of medicaments for the treatment of Parkinson disease.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Use

The present invention relates to the use of 5-HT_6 receptor antagonist compounds in the treatment of certain CNS disorders. More particularly the invention relates to the use of such compounds in the treatment of Parkinson's disease.

Parkinson's Syndrome refers to a collection of neurodegenerative diseases that are characterised by a disturbance of voluntary movement, and which includes both Idiopathic Parkinson's disease and Multiple System Atrophy. Typical features of these diseases are that muscles become stiff and sluggish, movement becomes clumsy and difficult and uncontrollable rhythmic twitching of groups of muscles produces characteristic shaking or tremor. Parkinson's disease is also associated with cognitive dysfunction and, in a proportion of cases, concurrent dementia. These conditions are believed to be caused by extensive degeneration of the dopaminergic nigrostriatal tract. The absence of adequate release of the chemical transmitter dopamine during neuronal activity thereby leads to the Parkinsonian symptomatology.

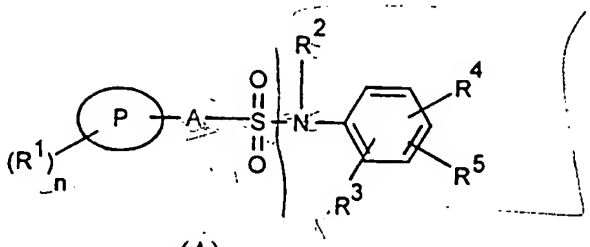
WO 98/27081, WO 98/27058 and WO 99/02502 all disclose compounds that are said to possess 5-HT_6 receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders. EPA 0815861 and EP 0930302 disclose sulphonamide and sulphone compounds respectively that are to said to possess 5-HT_6 receptor antagonist activity and are claimed to be useful in the treatment of various CNS disorders including Parkinson's disease. EP 0299602B1 discloses certain indolone derivatives that are useful in the treatment of Parkinson's disease and, advantageously, have anti-depressant and anxiolytic effects.

It has now been found that certain compounds, known in the art as 5-HT_6 receptor antagonists, selectively increases activity of the nigrostriatal pathway and consequently have utility in the treatment of Parkinson's disease. In addition, the compounds of the present invention have additional effects on the central nervous system, namely, cognitive effects. In particular, the cognitive effects of the compounds of the present invention are perceived to be advantageous as patients receiving current therapies often also need to take separate medication for the treatment of cognitive dysfunction and dementia. The presence of such qualities as a single compound may therefore reduce the need for such separate therapies.

The present invention therefore provides, in a first aspect, the use of a compound having 5-HT_6 receptor antagonist activity in the manufacture of a medicament for use in the treatment of Parkinson's Disease characterized in that the compound having 5-HT_6

receptor antagonist activity is selected from the group consisting of a compound of formula (A), (B) or (C)

Compound of Formula (A)



(A)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6,

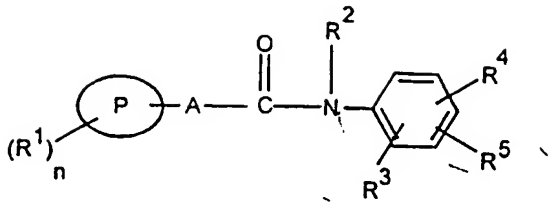
R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N- C_{1-6} alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl.

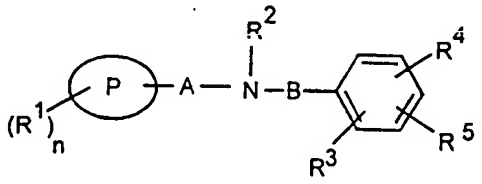
Compounds of Formula (B)



(B)

where R^1 – R^5, P, A and n are as defined in formula (A)

Compounds of Formula (C)



(C)

wherein:

P is phenyl, naphthyl, anthracenyl, a bicyclic heterocyclic ring, a tricyclic heteroaromatic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

B is SO_2;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more fluorine atoms, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, nitro, cyano, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6}alkyl or optionally substituted phenyl, SR^{11} where R^{11} is as defined above or R^1 is optionally substituted phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur, or R^1 together with a second R^1 substituent forms a group -O-CH_2-O-, OCH_2CH_2O-, -$CH_2CH_2CH_2$– or -$CH_2CH_2CH_2CH_2$-,

n is 0, 1, 2, 3, 4, 5 or 6;

R^2 is hydrogen, C_{1-6}alkyl, arylC_{1-6} alkyl or together with group P form a 5 to 8 membered ring optionally substituted with one or more C_{1-6}alkyl groups;

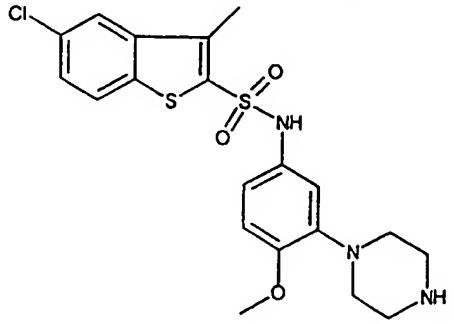
R^3 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy optionally substituted with one or more fluorine atoms, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, , nitro, trifluoromethyl, cyano or aryl or together with the group R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N-alkyl and p is 0 to 6 and R^6 is an optionally substituted 4- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or arylC_{1-6}alkyl; and

R^5 is a group R^3 or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups.

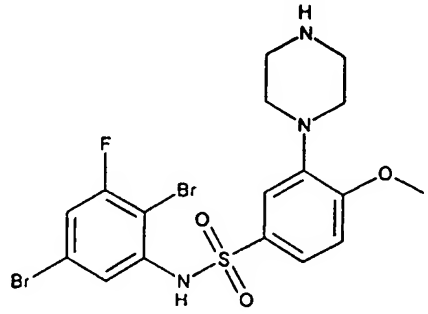
The preferred compounds for use in this invention demonstrate greater than 100-fold selectivity for 5-HT_6 receptors over other binding sites within the CNS, in particular, other 5-HT receptor sub-types and dopaminergic receptors. The selectivity of the compounds of this invention for 5-HT_6 receptors can be determined using binding assays methods which are well known to those skilled in the art.

Particularly preferred compounds of this invention include 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide (Example 83 in WO 98/27081), that is to say, the compound of formula (I)



(I)

and *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide (Example 140 in WO 99/02502) that is to say, the compound of formula (II)



(II)

It will be apparent to those skilled in the art that compounds of formulas (A), (B) and (C) may form acid addition salts. Suitable examples include pharmaceutically

acceptable salts such as maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Suitably, a compound of formula (I) or formula (II) is used as the hydrochloride salt.

Certain compounds of formulas (A), (B) and (C) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The compounds of formulas (A), (B) and (C) and their pharamaceutically acceptable salts can be prepared by the methods described in WO 98/27081, WO 98/27058 and WO 99/02502 respectively.

The compounds for use in this invention can be evaluated for anti – Parkinson activity using procedures known to those skilled in the art such as the MPTP treated marmoset model.

The compounds for use in this invention are expected to have utility in treating any condition characterized by degeneration of the dopaminergic nigrostriatal tract. Consequently, these compounds will be useful in the treatment of both Idiopathic Parkinson's disease and Multiple System Atrophy. Multiple System Atrophy includes olivopontocerebellar atrophy, striato-nigral degeneration type and Shy-Drager type atrophy.

The present invention further provides a method of treatment of Parkinson's Disease and other related disorders which comprises administering to a host in need thereof an effective amount of a compound of formula (A), (B) or (C) or a pharmaceutically acceptable salt thereof.

It will be appreciated by those skilled in the art that the compounds according to this invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, by co-administration with other anti-Parkinson's agents. Examples of such include levodopa or a dopamine agonists, and in particular, those described in EP 0299602B1.

When used in therapy, the compounds of formula (A), (B) or (C) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

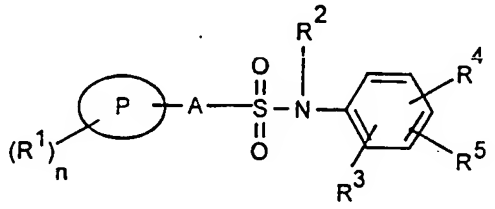
For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Suitably the compounds for use in this invention will be administered for a period of continuous therapy.

Claims:

1. The use of a compound having 5-HT_6 receptor antagonist activity in the manufacture of a medicament for use in the treatment of Parkinson's Disease characterized in that the compound having 5-HT_6 receptor antagonist activity is selected from the group consisting of a compound of formula (A), (B) or (C)

Compound of Formula (A)



(A)

wherein:

P is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, amino, C_{1-6}alkylamino or diC_{1-6}alkylamino, cyano or R^1 is phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

n is 0, 1, 2, 3, 4, 5 or 6,

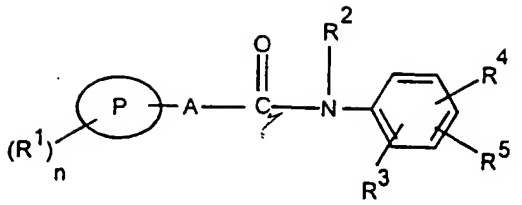
R^2 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ or R^3 is linked to R^2 to form a group $(CH_2)_2$ or $(CH_2)_3$;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N- C_{1-6} alkyl and p is 0 to 6 and R^6 is an optionally substituted 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl; and

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, nitro, trifluoromethyl, cyano or aryl.

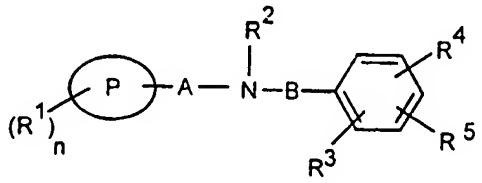
Compounds of Formula (B)



(B)

where $R^1 - R^5$, P, A and n are as defined in formula (A)

Compounds of Formula (C)



(C)

wherein:

P is phenyl, naphthyl, anthracenyl, a bicyclic heterocyclic ring, a tricyclic heteroaromatic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

B is SO_2;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more fluorine atoms, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, nitro, cyano, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6}alkyl or optionally substituted phenyl, SR^{11} where R^{11} is as defined above or R^1 is optionally substituted phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur, or R^1 together with a second R^1 substituent forms a group -O-CH_2-O-, OCH_2CH_2O-, -$CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2$-,

n is 0, 1, 2, 3, 4, 5 or 6;

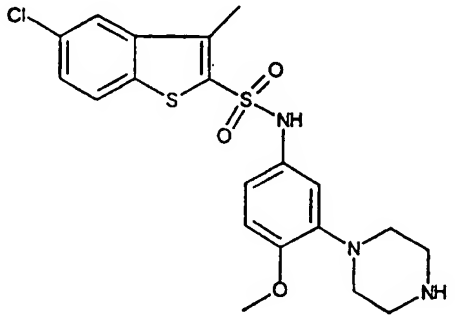
R^2 is hydrogen, C_{1-6}alkyl, arylC_{1-6} alkyl or together with group P form a 5 to 8 membered ring optionally substituted with one or more C_{1-6}alkyl groups;

R^3 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy optionally substituted with one or more fluorine atoms, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, , nitro, trifluoromethyl, cyano or aryl or together with the group R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups;

R^4 is $-X(CH_2)p-R^6$ where X is a single bond, CH_2, O, NH or N-alkyl and p is 0 to 6 and R^6 is an optionally substituted 4- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, or R^6 is NR^7R^8 where R^7 and R^8 are independently hydrogen, C_{1-6}alkyl or arylC_{1-6} alkyl; and

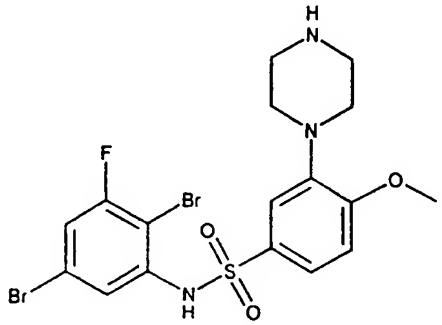
R^5 is a group R^3 or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$ optionally substituted with 1 or more C_{1-6}alkyl groups.

2. The use according to claim 1 wherein the 5-HT_6 receptor antagonist is the compound of formula (I) - 5-Chloro-3-methylbenzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-ylphenyl) amide or a pharmaceutically acceptable salt thereof



(I)

3. The use according to claim 1 wherein the 5-HT_6 receptor antagonist is the compound of formula (II) - *N*-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide or a pharmaceutically acceptable salt thereof



(II)

4. A pharmaceutical composition for use in the treatment of Parkinson's Disease which comprises a compound described in any one of claims 1 - 3 and a pharmaceutically acceptable carrier.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/495, 31/18, 31/165, A61P 25/16 — A3

(11) International Publication Number: **WO 00/12623**

(43) International Publication Date: 9 March 2000 (09.03.00)

(21) International Application Number: PCT/EP99/06219

(22) International Filing Date: 25 August 1999 (25.08.99)

(30) Priority Data:
9818914.5 28 August 1998 (28.08.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TX8 9EP (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: ROUTLEDGE, Carol [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WATERS, David, Martin; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
24 August 2000 (24.08.00)

(54) Title: USE OF 5-TH RECEPTOR ANTAGONISTS FOR THE TREATMENT OF PARKINSON'S DISEASE

(57) Abstract

Use of 5-HT_6 receptor antagonists for the preparation of medicaments for the treatment of Parkinson disease.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/EP 99/06219

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/495 A61K31/18 A61K31/165 A61P25/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 27081 A (BROMIDGE STEVEN MARK ;KING FRANCIS DAVID (GB); SMITHKLINE BEECHAM) 25 June 1998 (1998-06-25) cited in the application * See example N. 83 * page 9, line 33 -page 10, line 8; claims ---	1,3,4
P,Y	WO 99 02502 A (MOSS STEPHEN FREDERIK ;BROMIDGE STEVEN MARK (GB); SMITHKLINE BEECH) 21 January 1999 (1999-01-21) * See example N. 140 * page 1; claims --- -/--	1,2,4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2000	21.06.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/06219

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 815 861 A (HOFFMANN LA ROCHE) 7 January 1998 (1998-01-07) cited in the application page 3, line 52,53 page 3, line 57 page 39, line 48; claims	1,4
Y		1,2,4
Y		1,3,4

P,Y	BROMIDGE ET AL: "5-Chloro-N-(4-methoxy-3-piperazin-1-yl-ph enyl)-3-methyl-2-benzothioph enesulfonamide(SB-271046): A Potent, Selective, and Orally Bioavailable5-HT6 Receptor Antagonist" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 42, no. 2, 28 January 1999 (1999-01-28), pages 202-205-205, XP002109186 ISSN: 0022-2623 the whole document	1-4

P,Y	SLEIGHT ET AL: "The 5-hydroxytryptamine-6 receptor: localisation and function" EXPERT OPINION ON THERAPEUTIC PATENTS,GB,ASHLEY PUBLICATIONS, vol. 8, no. 10, 1 October 1998 (1998-10-01), pages 1217-1224, XP002093843 ISSN: 1354-3776 the whole document	1-4

P,X	WO 99 37623 A (BROMIDGE STEVEN MARK ;MOSS STEPHEN FREDERICK (GB); SMITHKLINE BEEC) 29 July 1999 (1999-07-29) page 1, line 9 -page 2, line 31; claim 9	1,4

A	EP 0 533 267 A (GLAXO GROUP LTD) 24 March 1993 (1993-03-24) page 5, line 1-8; claims 1,17	1-4

A	DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL GUPTA Y.K. ET AL: "Therapeutic potentials of 5-HT receptor modulators." retrieved from STN Database accession no. 94205555 XP002133179 abstract & INDIAN JOURNAL OF PHARMACOLOGY, (1994) 26/2 (94-107).,	1-4

	-/--	

2

INTERNATIONAL SEARCH REPORT

Interr ·ial Application No
PCT/EP 99/06219

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	BOURSON, ANNE ET AL: "Involvement of 5-HT6 receptors in nigro-striatal function in rodents" BR. J. PHARMACOL. (1998), 125(7), 1562-1566,1998, XP000900090 the whole document	1-4

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1,4 (partial); 2,3 (complete).

Use of compounds chemically defined by the Markush formula (A) in claim 1, in the manufacture of a medicament for the treatment of Parkinson's Disease.

2. Claims: 1,4 (partial).

Use of compounds chemically defined by the Markush formula (B) in claim 1, in the manufacture of a medicament for the treatment of Parkinson's Disease.

3. Claims: 1,4 (partial).

Use of compounds chemically defined by the Markush formula (C) in claim 1, in the manufacture of a medicament for the treatment of Parkinson's Disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/06219

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see FURTHER INFORMATION PCT/ISA/210

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1,4 (partial) 2,3 (complete)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,4 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mentioned in the description at page 4, in claims 2,3 with due regard to the general idea underlying the application.
Remark: the expression "a C1-6 alkylene group" is not clear.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat al Application No
PCT/EP 99/06219

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9827081 A	25-06-1998	AU 6090498 A	15-07-1998
		BG 103530 A	31-01-2000
		CN 1246116 A	01-03-2000
		CZ 9902203 A	17-11-1999
		EP 0946539 A	06-10-1999
		NO 993003 A	18-06-1999
		PL 334337 A	28-02-2000
WO 9902502 A	21-01-1999	AU 9257898 A	08-02-1999
		EP 0994862 A	26-04-2000
		NO 20000108 A	10-01-2000
EP 0815861 A	07-01-1998	AU 694696 B	23-07-1998
		AU 2841697 A	22-01-1998
		BR 9703788 A	17-11-1998
		CA 2209018 A	28-12-1997
		CN 1170574 A	21-01-1998
		CZ 9702002 A	14-01-1998
		HK 1007865 A	30-04-1999
		HR 970349 A	30-04-1998
		HU 9701096 A	01-02-1999
		JP 10067734 A	10-03-1998
		NO 972983 A	29-12-1997
		NZ 328146 A	28-10-1999
		PL 320822 A	05-01-1998
		US 6030976 A	29-02-2000
		US 5932599 A	03-08-1999
		US 5939451 A	17-08-1999
WO 9937623 A	29-07-1999	NONE	
EP 0533267 A	24-03-1993	AU 2452892 A	25-03-1993
		AU 2568792 A	27-04-1993
		CA 2078507 A	19-03-1993
		CN 1073430 A	23-06-1993
		CZ 9400611 A	16-11-1994
		WO 9306084 A	01-04-1993
		FI 941261 A	17-03-1994
		JP 6107637 A	19-04-1994
		MX 9205278 A	01-03-1993
		NO 940974 A	17-03-1994
		US 5358948 A	25-10-1994
		ZA 9207106 A	17-03-1994